

**Phase III, Randomized,  
Double Blind, Placebo  
Controlled Trial of Oral  
Suberoylanilide Hydroxamic  
Acid (Vorinostat) for  
Patients with Mesothelioma**

# Mesothelioma

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- Cancer of the membrane around the lung.
- 2,000 new cases per year
- 70-80% linked to asbestos
- Most patients diagnosed at Stages II to IV when treatment is palliative.

# Current Treatments

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- Surgery—resect operable lesions
- Radiation
- Systemic chemotherapy
  - Standard first line treatment
    - Pemetrexed—antifolate
    - Cisplatin

This combination has median survival of 12 months.

# New Drug—Vorinostat

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- Vorinostat—suberoylanilide hydroxamic acid
- Inhibitor of histone deacetylase—HDAC—which is an enzyme that removes acetyl groups from histones.
- Acetylation of histones regulates gene transcription.
- Low acetylation reduces gene transcription
- High acetylation opens DNA and increases gene transcription.
- Inhibitions of HDAC produces high acetylation and gene transcription.

# New Drug—Vorinostat

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- Oral
- Good bioavailability
- Toxicology in rats and dogs
  - Main toxicities were weight loss, leukopenia, thrombocytopenia, GI irritation.
  - Toxicities were rapidly reversible with stopping drug.
  - No cardiac damage or damage to other organs.

# New Drug—Vorinostat

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- Human trials—over 200 patients in 10 Phase I and II trials.
- Tolerability determined by total daily dose and number of consecutive days. Tried in many combinations
  - MTD 400 mg per day continuously
  - MTD 300 mg BID for 3 days per week
  - MTD 250 mg TID for 14 days on and 7 days off

# New Drug—Vorinostat

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- Human trials—over 200 patients in 10 Phase I and II trials.
  - Fatigue 81% Grade 4 1%
  - Nausea 64%
  - Hyperglycemia 61%
  - Diarrhea 53%
  - Anorexia 50%
  - Leukopenia 4% (Grade 3 or 4)
  - Thrombocytopenia 12% (Grade 3 or 4)
  - Anemia 9% (Grade 3 or 4)

# New Drug—Vorinostat

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- Many responses in Phase I and II trials
  - Leukemia or MDS 1 CR of 14 patients
  - Multiple Myeloma 4 SD of 7 patients
  - Lymphoma 1 CR, 1 PR of 7 pts.
  - Mesothelioma 2 responses of 13 pts



# Trial

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- Hypotheses: Compared to placebo, Vorinostat will
  - 1) Improve overall survival
  - 2) Improve response rate
  - 3) Improve progression free survival
  - 4) Improve dyspnea and FVC after Cycle #4

# Trial

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- Randomized trial of 660 patients with mesothelioma whose cancer has progressed through pemetrexed/platin.
- Patients can have had only 2 prior chemotherapy regimens.
- 18 years of age
- Karnofsky performance status of 70 or more
- Adequate bone marrow, kidney, liver function.

# Trial

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- Patient randomized to either
  - Vorinostat 300 mg BID on 3 days per week.
  - or
  - Placebo
- Patients in both arms get best supportive care.
- Primary endpoint is survival.

# Trial

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- Response to treatment by CT scan will be assessed every 6 weeks.
- Tumor samples will be used for molecular profiling.
- Blood samples collected for future genetic research focused on cancer.

# Study Visits

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- Visit 1—Screening
  - PE, Vital signs, EKG, PFTs, CT scan
  - Serum glucose, insulin, HB A<sub>1C</sub>
  - QOL and dyspnea assessments
- Visit 2—Drug administration
  - Consume first dose of drug in clinic
- Visits 3 and 4—Day 8 and 15—Adverse event assessment

# Study Visits

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- Visit 5—Day 21—Cycle #2 Return for Drug
- Visit 6—Day 15 of Cycle #2

Every 2 cycles –6 weeks—assessment of tumors by CT scan.

# Tests

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- Screening      PE, vital signs, PS,  
Lab tests—CBC,  
coagulation, urinalysis,  
LFTs, PFTs, EKG, etc.
- Cycle 1      Vital signs, PS, Lab tests,  
Days 1, 8, 15      PFTs, EKG, adverse events

Subsequent cycles only Days 1 and 15.

# Power and Sample Size

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- Primary endpoint is survival.
- With  $\alpha=0.05$  and  $\beta=90\%$  and 25% reduction in mortality or extension of life by 1.8 months:
- Need 540 deaths.



# Interim Analyses

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- Three interim analyses
  - After 50 patients have been on trial for 18 weeks.  
Question: Is vorinostat not active?
  - After 220 patients have been on trial for 18 weeks.  
Question: Is vorinostat better than placebo based on secondary endpoints?
  - After 270 deaths. Question: Is trial futile?